

Human chorionic gonadotropin value and its change prior to methotrexate treatment can predict the prognosis in ectopic tubal pregnancies

Koichi Watanabe | Yoshitsugu Chigusa  | Eiji Kondoh | Haruta Mogami |
Akihito Horie | Tsukasa Baba | Masaki Mandai

Department of Gynecology and
Obstetrics, Kyoto University, Kyoto, Japan

Correspondence

Yoshitsugu Chigusa, Department of
Gynecology and Obstetrics, Kyoto
University, Kyoto, Japan.
Email: chigusa@kuhp.kyoto-u.ac.jp

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Abstract

Purpose: To investigate the role of beta-human chorionic gonadotropin (HCG) level and its change prior to methotrexate (MTX) treatment as predictors of treatment success and to access the posttreatment observation period for ectopic tubal pregnancy.

Methods: Clinical data of 41 females treated with MTX for tubal pregnancies were reviewed and analyzed retrospectively.

Results: Among 41 patients, 34 achieved complete resolution without surgery. No statistically significant difference was observed in the presence of hemorrhagic ascites, serum progesterone levels, or diameters of adnexal mass between the MTX success and failure groups. Serum HCG levels on the day of MTX administration (day 1) were significantly lower in the MTX success group. Moreover, % HCG change per day, which represents the increment ratio of HCG prior to MTX treatment, was significantly lower in the MTX success group. Receiver operating characteristic (ROC) curves demonstrated that the treatment success was predicted by % HCG change per day less than +12.6% per day with a sensitivity of 87% and a specificity of 71%. The duration from treatment to complete recovery was strongly correlated with day 1 HCG levels.

Conclusions: Pretreatment HCG change is a significant predictor of therapeutic success of MTX treatment, and the treatment period may be predicted from initial HCG levels.

KEYWORDS

early pregnancy, ectopic pregnancy, human chorionic gonadotropin, methotrexate, tubal pregnancy

1 | INTRODUCTION

Ectopic pregnancy is a major cause of maternal morbidity and even mortality in the first trimester of pregnancy, and in these pregnancies, 97% of them are implanted within the fallopian tube. Recently, early diagnosis of ectopic pregnancy is feasible with transvaginal ultrasound and serial human chorionic gonadotropin (HCG) measurements. Once the diagnosis of an ectopic pregnancy is made, it is necessary to evaluate the appropriate treatment method immediately to prevent tubal rupture and to reduce maternal mortality. In addition to surgical intervention, medical therapy with methotrexate (MTX) for tubal pregnancy can be used in appropriately selected women with significant therapeutic success.¹ Although many treatment protocols have been suggested, the protocol most widely used is the “single dose protocol” introduced by Stovall.²

Upon commencement of MTX treatment for tubal pregnancy, the success rate and follow-up period are major concerns. While MTX treatment is a noninvasive strategy and can avoid surgery, it sometimes fails, contrary to expectation. However, it has been challenging to predict the precise clinical course after MTX treatment and to determine which patients could be treated with MTX successfully. After MTX treatment, circulating HCG levels are temporarily increased. Although several studies have demonstrated that the serum levels of HCG,³ as well as its increasing trend, might reflect the activity of the trophoblastic tissues and its response to MTX treatment,^{4–6} this notion has not been thoroughly investigated to date. Furthermore, patients who received MTX treatment require long-time observation until HCG levels decrease to a cutoff value because surgical intervention may be indicated due to tubal rupture or other reasons even several weeks after MTX injection.⁷ It must be beneficial for both patients and clinicians to estimate the follow-up period in advance.

Therefore, the purpose of the present study was to investigate the role of HCG levels and its increase prior to MTX treatment as predictors of treatment success and to access the posttreatment observation period for ectopic pregnancy, particularly in the context of tubal pregnancy.

2 | MATERIALS AND METHODS

We retrospectively reviewed patients of tubal ectopic pregnancies treated with a single-dose MTX protocol at Kyoto University Hospital between January 2006 and August 2016. The diagnosis was based on the patient's medical history, a clinical examination, the serum levels of total beta-human chorionic gonadotropin (β -hCG), which we refer to as HCG, transvaginal ultrasonography, and magnetic resonance imaging (MRI).

In our hospital, the basic indication criteria for MTX treatment were as follows: (a) hemodynamically stable, (b) no fetal cardiac activity detected on transvaginal ultrasound, (c) serum HCG concentration >1000 and ≤ 5000 mIU/mL, and (d) no contraindication for MTX treatment. The presence of a small to moderate amount

of ascites in hemodynamically stable females was not a contraindication for MTX therapy. To all patients meeting these criteria, we proposed MTX treatment, as well as surgical treatment, and selected the treatment option based on the patients' wishes. Several patients with a strong desire for MTX treatment were also included, despite HCG >5000 mIU/mL. In principal, we proposed the expectant management as the first-choice strategy to the patients whose serum HCG levels were not >1000 mIU/mL. However, several patients strongly requested medical management with MTX, and in those cases, we performed the MTX treatment after obtaining informed consent. The protocol of MTX treatment was based on a previous study² with a single dose of intramuscular injection of MTX 50 mg/m² at day 1. If the decline in HCG between day 4 and day 7 was $<15\%$, then a second dose of MTX was administered on day 7. In general, although not in all cases, the serum HCG levels were monitored until they reached less than the cutoff value (<0.5 mIU/mL).

We defined MTX treatment failure as cases requiring surgical management. Several clinical parameters, including progesterone levels, diameters of adnexal mass, presence of hemorrhagic ascites, and initial HCG values, were compared between the successful group and the failure group.

We also analyzed the changes in HCG levels per day before and after treatment and investigated the significance of pretreatment HCG increase. The rate of HCG increase or decrease prior to MTX treatment, which is referred to as the % HCG change per day in this study, was defined as follows: The percentage change in HCG levels between the most recent measurement day prior to MTX administration and the day of MTX treatment was divided by the observed time between measurements (ie, when HCG on the MTX treatment day [day 1] was 3000 mIU/mL and day -1 HCG was 2400 mIU/mL, % HCG change per day was $[3000-2400]/[1 - (-1)]/3000 \times 100 = +10\%$). We defined the day of MTX treatment as day 1, the day before MTX treatment as day 0, the day before day 0 as day -1, and so on.

The Wilcoxon rank-sum test was used to compare continuous variables between the success and failure groups. ANOVA analysis and Tukey's test were used to compare such variables among the three groups: successful with only single MTX, successful with second MTX, and the failed group. The chi-square test was used to compare categorical variables. The best cutoff value for % HCG change per day was obtained using the receiver operating characteristic (ROC) curve method. A P -value of <0.05 was considered to be statistically significant.

This study was approved by the ethics committee of Kyoto University (Registration number: R1010).

3 | RESULTS

During the study period, 137 females were admitted to our hospital with the diagnosis of tubal pregnancy. Figure 1 shows the patient details. Of the 137 patients, 41 patients received medical management with MTX. Among these patients, 34 patients (83%) achieved

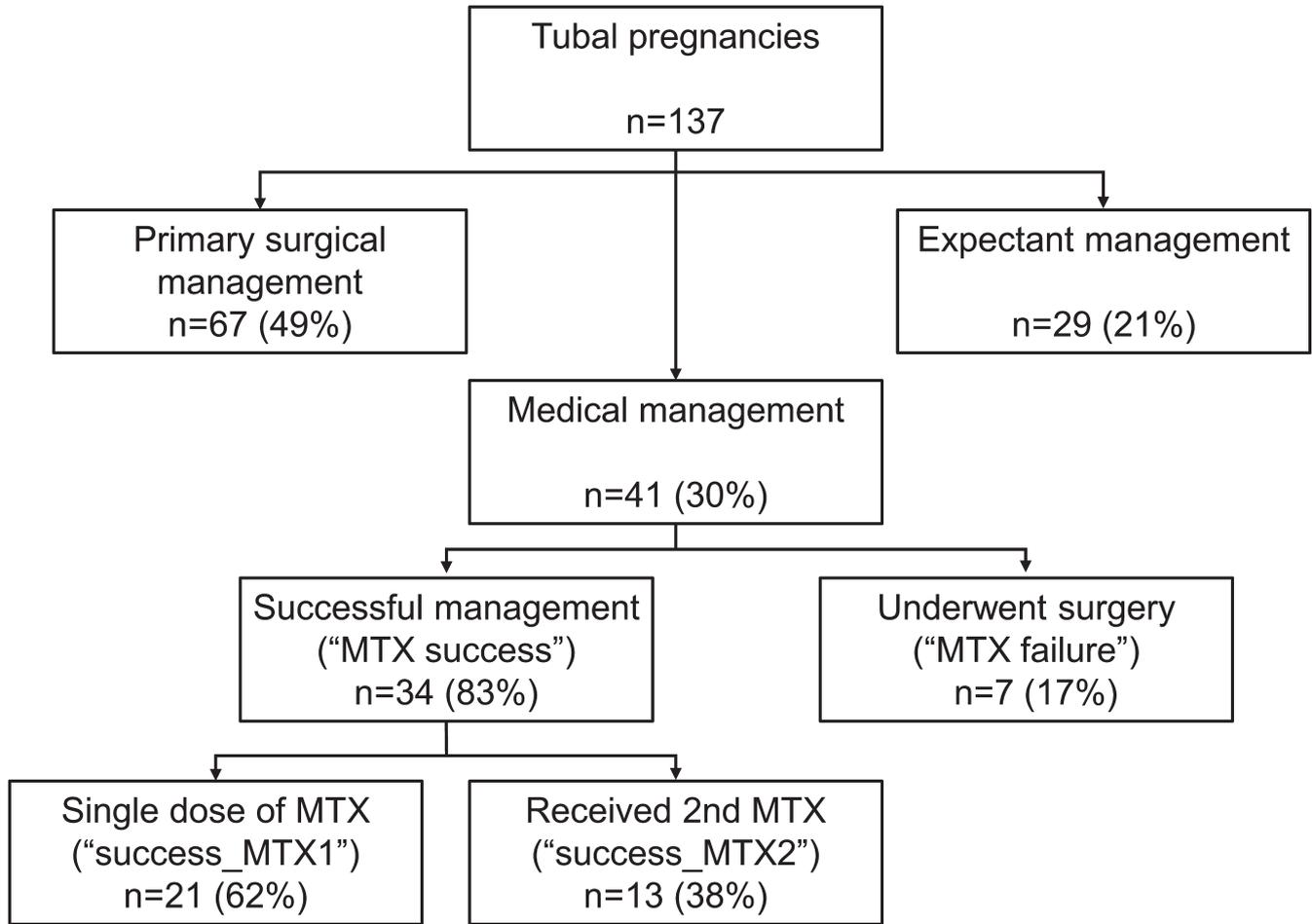


FIGURE 1 Flow diagram of patients included in the study

TABLE 1 Clinical characteristics of tubal pregnancy cases requiring surgery despite MTX treatment

Case	HCG at 1st injection of MTX (mIU/mL)	Time from 1st injection of MTX to surgery (d)	Final HCG before surgery (mIU/mL)	Cause of surgery
1	6796	2	—	Emergence of fetal cardiac activity
2	4191	10	9225	Emergence of fetal cardiac activity
3	2770	8	4809	Emergence of fetal cardiac activity
4	2741	5	5298	Increase in hemorrhagic ascites due to tubal abortion
5	2456	15	183	Increase in hemorrhagic ascites due to tubal abortion
6	4173	17	1595	Increase in hemorrhagic ascites due to tubal abortion
7	2779	9	2320	Increase in hemorrhagic ascites due to tubal rupture

HCG, serum levels of total beta-human chorionic gonadotropin; MTX, methotrexate.

complete resolution without surgical intervention (MTX success; n = 34, age; 35.0 ± 5.2 years old, gestational age; 7.2 ± 1.2 weeks of gestation, mean ± standard deviation, the same shall apply hereinafter). Of the successful patients, 21 patients (62%) were treated with

a single dose of MTX (Success_MTX1; n = 21, age; 35.0 ± 5.5 years old, gestational age; 7.2 ± 1.3 weeks of gestation), and the remaining 13 patients (38%) required a second dose of MTX (Success_MTX2; n = 13, age; 35.1 ± 5.0 years old, gestational age; 7.2 ± 1.2 weeks of

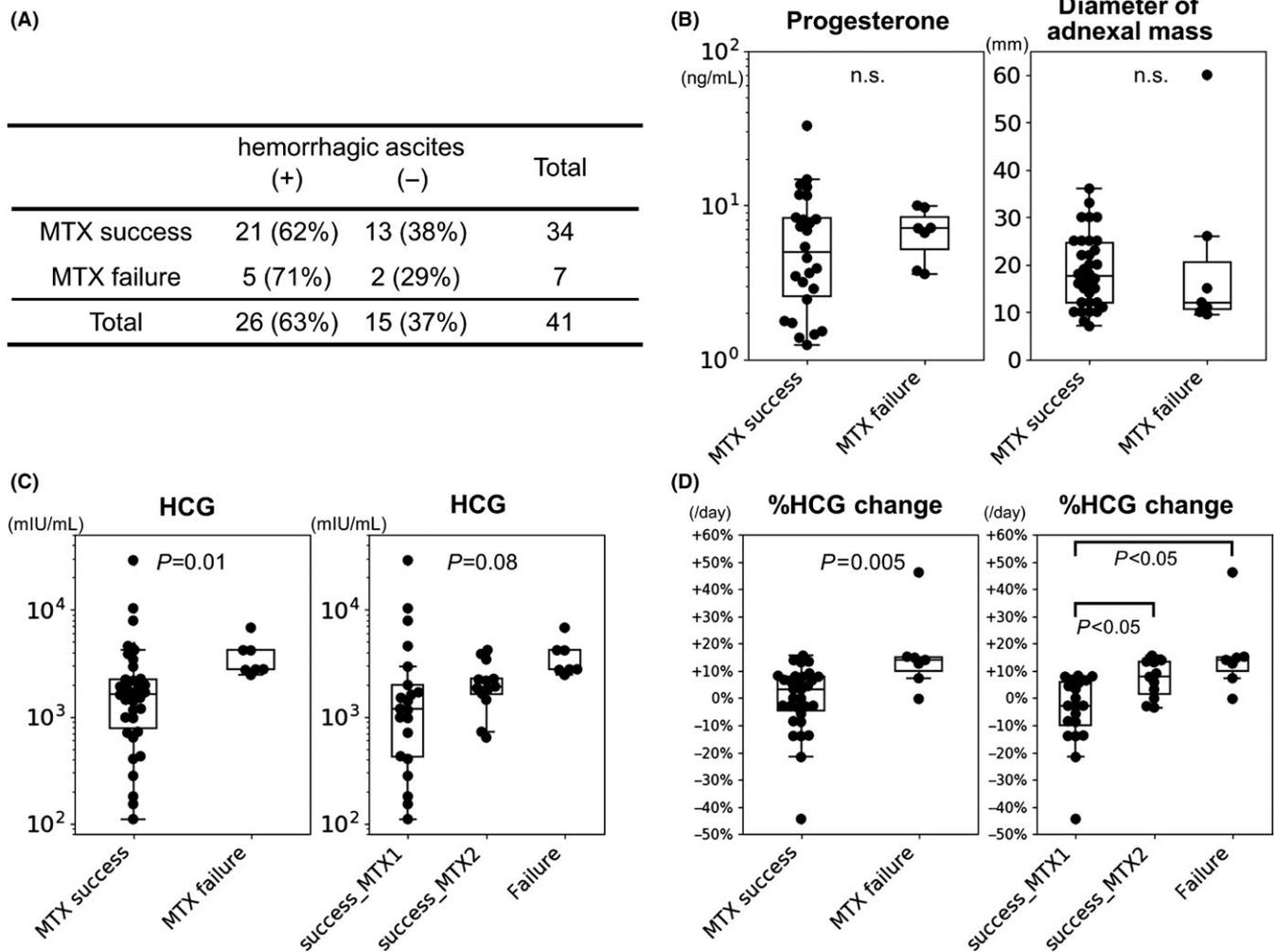


FIGURE 2 Clinical factors relevant to the success of MTX treatment. A, Presence of hemorrhagic ascites; B, serum progesterone levels and diameters of adnexal mass at the start of MTX treatment; C (left), serum levels of HCG on day 1 of MTX treatment; and D (left), % HCG change per day prior to MTX treatment in MTX success group and failure group. C (right), serum levels of HCG on day 1 of MTX treatment; and D (right), % HCG change per day prior to MTX treatment were further analyzed in groups of success_MTX1 (single dose of MTX), success_MTX2 (received 2nd MTX), and MTX failure. Data are presented as the median value with interquartile range

gestation). No patient received more than two doses of MTX. In contrast, seven patients (17%) eventually required surgical management after MTX administration (MTX failure; $n = 7$, age; 31.4 ± 3.2 years old, gestational age; 6.4 ± 1.3 weeks of gestation). Table 1 shows the clinical characteristics of patients with MTX failure. Three patients required an operation due to the emergence of fetal cardiac activity, and the other four patients underwent surgery due to the appearance of peritoneal fluid or progressive anemia, suggesting hemorrhage due to tubal rupture.

To determine the predictive factors of clinical outcome for MTX treatment for tubal pregnancy, ultrasound findings and laboratory data of each patient were analyzed. First, the ratio of the presence of hemorrhagic ascites revealed by transvaginal ultrasound did not show a significant difference ($P = 0.21$; chi-square test) (Figure 2A). Second, between MTX success and MTX failure groups, no statistically significant difference was observed in the serum progesterone levels and diameters of adnexal mass at the start of MTX

treatment (Figure 2B). However, serum levels of HCG on day 1 were significantly lower in the MTX success group compared with those in the MTX failure group (median: 1624 vs 2779 mIU/mL, $P = 0.01$) (Figure 2C, left). However, ANOVA analysis did not show a significant difference between the Success_MTX1, Success_MTX2, and MTX failure groups (Figure 2C, right).

Next, to test if the trend of HCG levels reflects the prediction of treatment outcome, % HCG change per day was calculated. In the MTX success group, HCG levels decreases or increases were minimal in most cases. However, HCG levels were increased in nearly all cases in the MTX failure group. Consistent with these findings, the % HCG change per day prior to MTX treatment was significantly lower in the MTX success group than the MTX failure group (median: +3.1% vs +14.0% per day, $P = 0.005$) (Figure 2D, left). In the MTX success group, HCG levels were decreased in most of cases in the success_MTX1 group, whereas in the success_MTX2 group, there are more HCG-increased cases than HCG-decreased cases.

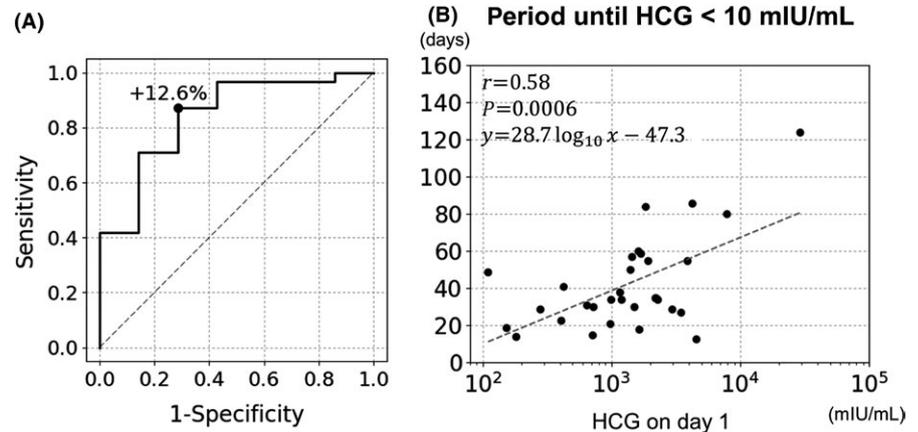


FIGURE 3 A, Receiver operating characteristic curve of % HCG change per day. B, Correlation between the period from the treatment to HCG <10 mIU/mL and HCG levels of day 1

Consequently, the % HCG change per day prior to MTX treatment in the Success_MTX1 group was significantly lower than patients in the Success_MTX2 group and MTX failure group. This result strongly suggested that an increasing trend of HCG might be an indicator of the refractory case.

Finally, to predict treatment success, the optimal cutoff level of pretreatment % HCG change per day was calculated from the ROC curve (Figure 3A). The area under the curve was 0.84, and the treatment success was predicted by % HCG change per day less than +12.6% per day with a sensitivity of 87% and a specificity of 71%.

After MTX treatment, we followed up patients in principle until HCG fell below the cutoff value (<0.5 mIU/mL). However, some patients stopped visiting our hospital for unknown reasons prior to reaching the cutoff value. Among the 34 patients in the MTX success group, 31 patients (91%) were followed up until at least HCG <10 mIU/mL. Thus, we analyzed the correlation between the period from treatment to HCG <10 mIU/mL and serum HCG levels of day 1, that is, the day of MTX administration. Consequently, this period was strongly correlated with day 1 HCG levels ($n = 31$, $r = 0.58$, $P = 0.0006$) (Figure 3B). Moreover, the period until HCG decreased to <10 mIU/mL can be predicted using the formula: $y = 28.7 \log_{10}(x) - 47.3$ (x is day 1 HCG level [mIU/mL], and y is the duration for HCG to become <10 mIU/mL).

4 | DISCUSSION

In the present study, we revealed that % HCG change per day could be a useful parameter to predict MTX treatment success for tubal pregnancy and that the estimated follow-up period could be calculated based on the initial HCG levels. These findings might directly contribute to the successful MTX treatment and safe posttreatment observation for tubal pregnancy in clinical practice.

Methotrexate has become the treatment of choice for hemodynamically stable ectopic pregnancies, and its efficacy for appropriately selected women has been confirmed in many studies. A success rate of 83% in the present study was consistent with previously reported success rates.^{2,8,9} Although several factors associated with successful MTX treatment have been investigated, the initial HCG

level appears to have the greatest prognostic value.³ The significance of initial HCG levels was also indicated in this study, whereas other factors, such as adnexal mass size, serum progesterone level, or the presence of hemorrhagic ascites, did not show a significant difference. The large size of the ectopic pregnancy (≥ 4 cm) is often used as a criterion for exclusion in medical treatment regimens.¹ In this study, all patients except one had the small ectopic mass (<4 cm). Although we did not use this exclusion criterion, no difference could be seen in this population. This finding is observed partly because most women in Japan visit a physician as soon as they are aware of amenorrhea, and consequently, the diagnosis of tubal pregnancy is usually made before a large ectopic mass emerges. The presence of hemorrhagic ascites may affect the choice of treatment, but past cases have shown that fluid-free pelvic cavity is not associated with medical treatment failure,³ which is consistent with the result of our study. In addition, serum progesterone levels also did not affect MTX treatment success, as demonstrated in this study and in previous studies.^{10,11}

Our result indicated that <12.6% of % HCG change per day might be a predictor of successful MTX treatment. This finding is consistent with those of previous studies. da Costa Soares et al⁵ and Cohen et al⁴ reported lower increases in the 48 hours before treatment as a predictor of success with a cutoff value of 11.1% and 12%, respectively. In a recent study of 69 patients, Levin et al⁶ found that HCG increases of <14% in the 24 hours prior to treatment were also strong predictor. Importantly, our study showed that % HCG change per day is a predictor of both single- and second-dose successful MTX treatments. Interestingly, we did not regard requiring a second administration of MTX as treatment failure, while previous studies made this categorization.⁴⁻⁶ The major benefit of MTX treatment would be the avoidance of surgical intervention, and for that purpose, the second dose of MTX is acceptable.

Another difference between this study and previous studies is the interval for HCG monitoring before the MTX injection. In previous studies, pretreatment HCG increases were measured at specific intervals of 24 or 48 hours. In contrast, we did not specify the HCG measuring interval and calculated the HCG increment ratio from the given measurements with varied intervals, such as normal clinical settings. From the result of the present study, clinicians can

immediately calculate an HCG increase given HCG measurements without waiting 24 or 48 hours and can determine the treatment of choice.

This study also noted the period of treatment and provides a formula to predict the period from pretreatment HCG levels. Although for the serum HCG level to decrease to the cutoff value takes as long as several months, this formula helps to predict the expected time to complete the observation and when to determine the appropriate interval of monitoring HCG. Overall, HCG surveillance should be continued until HCG reaches <0.5 mIU/mL because cases of tubal rupture have been reported despite HCG levels of <10 mIU/mL.¹² Thus, patients need to be informed of the risk of rupture and the potential emergent surgery during the observation period.

This study was limited due to its retrospective nature and the small number of patients. More prospective studies with a larger sample size are needed and may affect future treatment guidelines. In addition, we included some patients whose HCG levels were out of our original inclusion criteria. This might lead to selection bias.

In conclusion, the current study demonstrated the importance of pretreatment HCG levels and its dynamics for predicting the therapeutic success of MTX treatment and illustrated the method for the prediction of treatment period from initial HCG levels. HCG increases of <12.6% per day before MTX injection can be reassured for success, and the formula $y = 28.7 \log_{10}(x) - 47.3$ can be used to predict the treatment period.

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DISCLOSURES

Conflict of interest: Koichi Watanabe, Yoshitsugu Chigusa, Eiji Kondoh, Haruta Mogami, Akihito Horie, Tsukasa Baba, and Masaki Mandai declare that they have no conflict of interests. **Human rights statements and informed consent:** All the procedures were followed in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all the patients to be included in the study. **Animal studies:** This article does not contain any study with animal participants that were performed by any of the authors. **Approval by ethics committee:** This study was approved by the ethics committee of Kyoto University (Registration number: R1010).

ORCID

Yoshitsugu Chigusa  <http://orcid.org/0000-0001-9629-5912>

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